EXHIBIT B

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Letter to the Editor

Unified Nomenclature for Eph Family Receptors and Their Ligands, the Ephrins

The largest subfamily of receptor protein-tyrosine kinases consists of receptors related to Eph, a receptor named for its expression in an erythropoietin-producing human hepatocellular carcinoma cell line. This subfamily has received considerable attention as receptors and their ligands have been identified at a dizzying pace in recent years and implicated in cell–cell interactions involved in nervous system patterning, including axon guidance, and in other aspects of development. To date, fourteen distinct receptors of this subfamily and eight distinct ligands have been identified in warm-blooded vertebrates (mammals and birds), with many related proteins identified in cold-blooded vertebrates and in invertebrates.

Because of the rapid pace of discovery of receptors and ligands in various species, many different names have been used to designate them, making it difficult for the general scientific community to follow developments in this exciting field. To address this problem, representatives of over 20 laboratories involved in research on the Eph family initiated extensive discussions at the "Molecular Biology of Axon Guidance" workshop held at the EMBL, Heidelberg, in September, 1996. As a result, a proposal was put forth to unify and to systematize the nomenclature for these ligands and receptors, and an Eph Nomenclature Committee was elected to refine the proposal in consultation with the community at large. The resulting nomenclature has now been endorsed by over 70 scientists,[1] many of whom contributed extensively to defining the nomenclature and to preparing this letter, as well as by the Human and Mouse Gene Nomenclature Committees.

Ligands

It is proposed that the ligands be known as ephrins (pronounced eff-rins), which can be derived as an abbreviation for Eph family receptor interacting proteins or from the ancient Greek word εφορος (ephoros), meaning overseer or controller. The ligands are naturally divided into two structural types, being membrane-anchored either by a glycosylphosphatidylinositol (GPI) linkage or through a transmembrane domain. In addition, these two subgroups of ligands can be divided on the basis of their sequence relationships (Figure 1) and functionally on the basis of their preferential binding to two corresponding receptor subgroups, as described below. For this reason, it is proposed that the ligands be divided into the ephrin-A subclass, which are GPI-linked proteins, and the ephrin-B subclass, which are transmembrane proteins. The locus designations for human gene map positions for these two subclasses will be *EFNA* and *EFNB* (previously designated *EPLG*).

Receptors

It is proposed that the receptors be known as Eph receptors. The Eph family receptors can be divided into two groups based on the relatedness of their extracellular domain sequences (Figure 1). This grouping also appears to correspond to the ability of the receptors to bind preferentially to the ephrin-A or ephrin-B proteins. It is therefore proposed that the group that includes receptors interacting preferentially with ephrin-A proteins be called EphA (pronounced eff-A) and the group that includes receptors interacting preferentially with ephrin-B proteins be called EphB (pronounced eff-B). Human gene map locus names are *EPHA* and *EPHB*, respectively.

Numbering

Individual receptors and ligands within each subclass will be designated by an arabic numeral, assigned based on date of publication of an essentially full-length sequence. Current assignments for receptors and ligands are shown in Table 1. These assignments are based on sequences obtained in various warm-blooded vertebrate species, because of the observation of high sequence conservation across these species that allows unambiguous assignment of orthologs (homologs diverging by speciation rather than by gene duplication).

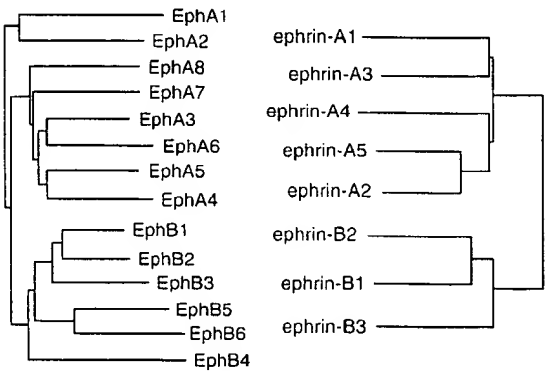

Figure 1. Sequence Homology Trees for Eph Receptors and Ephrins

The ephrin-A ligands are GPI-anchored proteins, whereas the ephrin-B ligands are transmembrane proteins. Dendrograms were produced with the Clustal program, using the extracellular domains of the receptors or the conserved core sequences of the ligands.

[1]The following scientists have endorsed the use of this nomenclature: D. J. Anderson, M. Barbacid, L. J. Berg, A.D. Bergemann, F. Bonhoeffer, B. Böhme, A. W. Boyd, A. W. Brändli, M. Bronner-Fraser, I. W. Caras, D. P. Cerretti, P. Chambon, P. Charnay, H.-J. Cheng, T. Ciossek, I. O. Daar, S. Davis, V. M. Dixit, U. Drescher, A. Faissner, J. G. Flanagan, F. A. Fletcher, G. M. Fox, J. Frisen, N.W. Gale, P. Gilardi-Hebenstreit, C. S. Goodman, A. Hemmati-Brivanlou, M. Henkemeyer, H. Hirai, N. Holder, S. J. Holland, T. Hunter, N. Ikegaki, R. Klein, S. A. Koblar, C. E. Krull, R. Lansford, G. Lemke, R. A. Lindberg, S. D. Lyman, P. C. Maisonpierre, C. Marcelle, G. C. Miescher, B. Monschau, N. A. Nicola, M. A. Nieto, K. Ohta, D. D. M. O'Leary, D. Orioli, E. B. Pasquale, T. Pawson, A. D. Reith, J. H. Rogers, B. M. Rohrer, J.R. Sanes, T. D. Sargent, J. B. Scales, B. Schindelholz, D. A. Siever, K. Strebhardt, H. Sugimura, H. Tanaka, X. X. Tang, M. Tessier-Lavigne, A. Ullrich, D. M. Valenzuela, M. F. Verderame, A. Wanaka, V. M. Watt, A. A. Welcher, D. G. Wilkinson, R. S. Winning, G. D. Yancopoulos, R. Zhou, A. Ziemiecki, S. L. Zipursky.

Table 1. Nomenclature for the Eph Receptor and Ephrin Families

Receptors		Ligands	
New Name	Previous Names	New Name	Previous Names
EphA1	Eph, Esk	ephrin-A1	B61; LERK-1, EFL-1
EphA2	Eck, Myk2, Sek2	ephrin-A2	ELF-1; Cek7-L, LERK-6
EphA3	Cek4, Mek4, Hek, Tyro4; Hek4	ephrin-A3	Ehk1-L, EFL-2, LERK-3
EphA4	Sek, Sek1, Cek8, Hek8, Tyro1	ephrin-A4	LERK-4; EFL-4
EphA5	Ehk1, Bsk, Cek7, Hek7; Rek7	ephrin-A5	AL-1, RAGS; LERK-7, EFL-5
EphA6	Ehk2; Hek12		
EphA7	Mdk1, Hek11, Ehk3, Ebk, Cek11		
EphA8	Eek; Hek3		
EphB1	Elk, Cek6, Net; Hek6	ephrin-B1	LERK-2, Elk-L, EFL-3, Cek5-L; STRA-1
EphB2	Cek5, Nuk, Erk, Qek5, Tyro5, Sek3; Hek5, Drt	ephrin-B2	Htk-L, ELF-2; LERK-5, NLERK-1
EphB3	Cek10, Hek2, Mdk5, Tyro6, Sek4	ephrin-B3	NLERK-2, Elk-L3, EFL-6, ELF-3; LERK-8
EphB4	Htk, Myk1, Tyro11; Mdk2		
EphB5	Cek9; Hek9		
EphB6	Mep		

Previous names are listed by publication date with full-length sequences shown first. Names after a semicolon indicate hypothetical orthologs or proposals to rename a sequence that had previously been published. While we recommend using the new nomenclature, initial identification references should be cited as appropriate.

Orthologs

Apparent orthologs in mammals and birds will be given the same name. The species can optionally be indicated by a small letter before the name (e.g., h-ephrin-A1 for human, m- for mouse, etc. . . .). Assignments for fish and amphibian proteins, which may largely coincide with those shown here, will be published elsewhere (details will be available at the Eph Nomenclature web site [http://www.eph-nomenclature.com]).

Naming New Sequences

A new member of the family is defined as a fully sequenced gene, cDNA, or protein that belongs to this subfamily based on sequence homology. Please consult the Eph Nomenclature web site prior to publication of any new member, apparent ortholog, gene locus, or splice variant to obtain details on how to assign an appropriate name and number.

We recommend that this nomenclature be used in future publications.

Eph Nomenclature Committee[2,3]

[2]The appropriate text citation for this letter in future publications is as follows: (Eph Nomenclature Committee, 1997).

[3]The committee consists of: J. G. Flanagan,* N. W. Gale,† T. Hunter,‡ E. B. Pasquale,§ and M. Tessier-Lavigne‖ (chair).

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